Devyser Thrombophilia

Art. No.: 8-A035

For *in-vitro* Diagnostic Use

Instructions for Use

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1. Introduction to Devyser Thrombophilia

Intended Use

The Devyser Thrombophilia kit is an in vitro diagnostic product for qualitative detection of genetic variants that may be associated with thrombophilia. The test can distinguish between individuals who are heterozygote and homozygote for all tested genetic variants.

The following alleles are detected:
- Factor V Leiden (normal and mutated)
- Factor V R2 (normal and mutated)
- Prothrombin/FII 20210 (normal and mutated)
- MTHFR 677 (normal and mutated)
- MTHFR 1298 (normal and mutated)
- PAI-1/Serpin 1 (4G and 5G)

Included in the Kit

Analysis of the different alles is performed using one single amplification mix (Thromb Mix).

Test Procedure

DNA extraction: The Devyser Thrombophilia kit has been validated using QIAamp DNA Blood Mini Kit (Qiagen, cat.# 51104) for extraction of DNA from human whole blood.

Amplification: The Devyser Thrombophilia kit has been validated using Life Technologies/ABI GeneAmp® System 9700 and Life Technologies Veriti® Thermal cycler.

Detection: Life Technologies/ABI Genetic Analyzers (ABI 310, 3100, 3130, 3500, 3730) that support detection of Devyser Dye-Set DEV-5.

Background

Thrombophilia is caused by abnormalities in blood coagulation that increases the risk of thrombosis (1, 2). These abnormalities are frequently seen in patients who have an episode of thrombosis that was not provoked by other causes (3). A significant proportion of the population has a detectable abnormality, but most of these only develop thrombosis in the presence of an additional risk factor (2).

Congenital thrombophilia is frequently caused by mutations in genes coding for coagulation factors such as factor V Leiden and prothrombin (1, 4, 5).

Common conditions associated with thrombophilia are deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE). Thrombophilia has also been linked to recurrent miscarriage (6, 7).

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Principle of the Procedure

The Devyser Thrombophilia kit is based on multiplex allele specific PCR amplification for detection of normal, (non-mutated) and mutated alleles in the following loci:
- Factor V Leiden
- Factor V R2
- Prothrombin/FII 20210
- MTHFR 677
- MTHFR 1298
- PAI-1/Serpin 1 4G/5G

Allele specific PCR amplification generates fluorescently labelled fragments that are analysed by capillary electrophoresis (CE) on a Genetic Analyzer instrument. Amplified fragments are identified based on size and fluorescent labels.

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2. Warnings and Precautions

A.

Devyser Thrombophilia has been validated using a total PCR reaction volume of 12,5 µL. Changing the reaction volume will compromise the kit performance.

B.

Avoid microbial contamination of ragents when removing aliquots from reagent vials. The use of sterile disposable aerosol barrier pipette tips is recommended.

C.

Do not pool reagents from different lots or from different vials of the same lot.

D.

Do not use a kit after its expiry date.

E.

Do not use opened or damaged kit reagent vials.

F.

Work flow in the laboratory should proceed in a unidirectional manner, beginning in the reagent preparation area and moving to the DNA extraction area and then to the amplification area and finally to the detection area. Pre-amplification activities should begin with reagent preparation and proceed to DNA extraction. Reagent preparation activities and DNA extraction activities should be performed in separate areas. Supplies and equipment should be dedicated to each activity and not used for other activities or moved between areas. Gloves should be worn in each area and should be changed before leaving that area. Equipment and supplies used for reagent preparation should not be used for DNA extraction activities or for pipetting or processing amplified DNA or other sources of target DNA. Amplification and detection supplies and equipment should remain in the amplification and detection area at all times.

G.

Handling of kit components and samples, their use, storage and disposal should be in accordance with the procedures defined by national biohazard safety guidelines or regulations.

H.

Wear powder free disposable gloves, laboratory coats and eye protection when handling specimens and kit reagents. Wash hands thoroughly after handling specimens and kit reagents.

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3. Symbols used on Labels

Lot or batch number

Expiry date

Number of tests

Store below temperature shown

Catalogue number

Manufacturer

In vitro diagnostic device

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4. Required Material

4.1 Included in the kit

Configuration

The Devyser Thrombophilia test kit contains reagents for analysis of 48 samples.

Components

Cap Colour	Tube Colour	Label	Art.Nr.	Kit Content
Orange	Clear	PCR Activator	4-A018	1
Turquoise	Amber	Thromb Mix	4-A213	1

4.2 Required but not Provided

Reagent Preparation

· Consumables for the Thermal Cycler
· Micropipette/dispenser with aerosol barrier tips or displacement tips
· Disposable protective gloves (powder free)

DNA Extraction

· Reagents and equipment according to manufacturer's instructions for use
· Micropipette/multipipette with aerosol barrier tips

Amplification

· Thermal Cycler: Life Technologies/ABI GeneAmp® PCR System 9700 and Life Technologies Veriti® Thermal cycler. For use of alternative thermal cyclers the following ramping rates must be applied: heating 1,6 ˚C/s, cooling 1,6 ˚C/s
· Micropipette/dispenser with aerosol barrier tips or displacement tips

Detection

· Life Technologies/ABI Genetic Analyzer (ABI 310, 3100, 3130, 3500, 3730)
· Performance optimized polymers: POP-4™ or POP-7™
· Hi-Di™ Formamide, Genetic Analysis Grade
· 1x Genetic Analyzer Buffer
· Micropipette/multipipette/dispenser with aerosol barrier tips or displacement tips

Size Standard

560 SIZER ORANGE (Devyser cat.# 8-A402) or GeneScan™ 600 LIZ® Size Standard (Life Technologies cat.# 4366589)

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4.3 Dye-Set Calibration

ABI 3100, 3130, 3730:
Use DEV-5 Dye-Set MultiCap kit (Devyser cat.# 8-A401) in the “Any5Dye” Dye-Set.

ABI 3500:
Use DEV-5 Dye-Set MultiCap kit (Devyser cat.# 8-A401) and generate the DEV-5 Dye-Set.

ABI 310 Matrix file generation:
Use DEV-5 Dye-Set SingleCap kit (Devyser cat.# 8-A400). Run with module file “GS STR POP4 (1 mL) G5.md5”

Detailed instructions for Dye-Set calibration may be downloaded from the download section at: http://www.devyser.com/qf-pcr-accessories/dev-5-calibrators.

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5. Storage and Handling Requirements

A.

Store all components below -18 °C.

B.

The activated reaction mix (prepared by addition of Thromb Mix to the PCR Activator tube) may be stored at +2 to +8 °C for at least 7 days and at below -18 °C for at least 90 days. Avoid repeated freeze-thawing.

C.

Dispose of unused reagents and waste in accordance with country, federal, state and local regulations.

D.

Do not mix reagents from different kit lot numbers.

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6. Sample Requirements

Clinical Samples

The Devyser Thrombophilia kit is for use with human genomic DNA extracted from whole blood.

DNA Extraction and Measurement

Preparation of DNA from whole blood samples

Results are consistently obtained with DNA extracted from human whole blood using QIAamp DNA Blood Mini Kit (Qiagen, cat.# 51104). Follow the protocol starting with 200 µL fresh whole blood and elute in 200 µL elution buffer. It is normally not necessary to determine the concentration of the purified DNA sample if this procedure is followed. The purified DNA can be used directly for PCR without any further dilution.

It is recommended that alternative DNA extraction methods and sample materials are thoroughly evaluated with the Devyser Thrombophilia kit prior to the results being used for diagnostic use. For the recommended PCR conditions and analysis settings (see sections 7.2- 7.3), results are consistently obtained at DNA concentrations between 25 and 150 ng/PCR reaction (10 - 60 ng genomic DNA/µL sample).

All DNA concentrations referred to in this handbook were determined using Qubit® dsDNA HS Assay Kit (Life Technologies, cat.# Q32851). The DNA concentration determined in a sample using Qubit® dsDNA HS Assay Kit may differ from the DNA concentration determined by other methods.

Procedure and Storage

According to manufacturer's instructions for use.

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7. Instructions for Use

7.1 Workflow Devyser Thrombophilia

Each Devyser Thrombophilia kit (art.# 8-A035) contains reagents for 48 samples. The activated reaction mix should be prepared before preparing the DNA samples if the complete process is performed in one day. The opposite order is advisable only if the DNA samples are prepared the day before amplification or earlier.

The activated reaction mix is prepared by adding the Thromb mix to the PCR Activator. It is recommended that the activated reaction mix is dispensed into appropriate PCR reaction tubes after preparation. Before dispensing ensure that the activated reaction mix is properly mixed (see below). Dispense in 10 µL aliquots and store at below – 18 °C.

Devyser Thrombophilia has been validated using a total PCR reaction volume of 12,5 µL. Changing the reaction volume will compromise the kit performance.

Ensure that the Thromb mix is completely thawed before use.

1. Centrifuge each tube briefly to collect the content. Do not vortex the tubes at this step.
2. Add 500 µL from the Thromb mix to the PCR Activator.
3. Carefully mix by pipetting several times from the bottom of each tube.
4. Vortex the activated reaction mix tube and centrifuge briefly to collect the content.
5. Add 10 µL of the activated reaction mix to separate PCR reaction tubes.
6. Cap the reaction tubes and centrifuge briefly to collect the contents.
7. Continue to step 7.2.

The activated reaction mix is stable at +2-8 °C for at least 7 days and at below -18 °C for at least 90 days. Avoid repeated freeze-thawing.

7.2 Sample Preparation and PCR Amplification

Sample Preparation

It is recommended that alternative DNA extraction methods and sample materials are thoroughly evaluated with the Devyser Thrombophilia kit prior to the results being used for diagnostic use. For the recommended PCR conditions and analysis settings (see below), results are consistently obtained at DNA concentrations between 25 and 150 ng/PCR reaction (10- 60 ng genomic DNA/µL sample). See also section 6.

Addition of Sample

Samples and controls should be added in a dedicated area separated from reagent preparation, amplification and detection areas.

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1. Add 2,5 µL of clinical sample (10 - 60 ng genomic DNA/µL sample) to each PCR reaction tube containing activated Thrombo mix (from step 7.1)
2. Cap the tubes and centrifuge briefly to collect the content.

Amplification

The Devyser Thrombophilia kit has been validated using Life Technologies/ABI GeneAmp® System 9700 and Life Technologies Veriti® Thermal cycler. Other PCR instruments should be tested and evaluated for optimal performance by the user before reporting results obtained with the Devyser Thrombophilia kit. PCR instruments should be regularly calibrated and maintained to ensure accurate PCR performance.

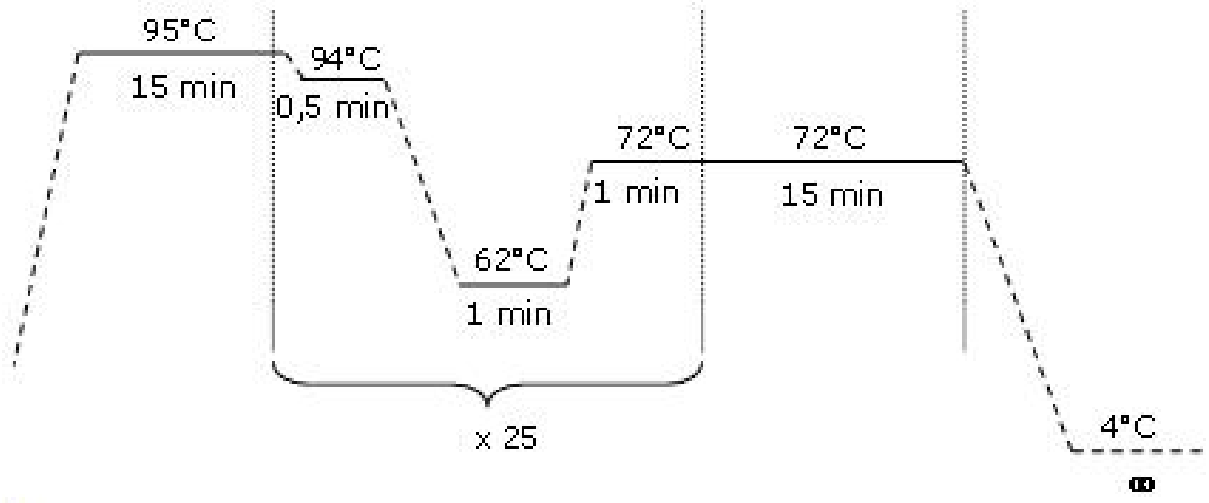
For Life Technologies GeneAmp® PCR System 9700: Set “ramp speed” to “MAX”.

For Life Technologies Veriti® Thermal cycler: In the "Tools Menu" select "Convert a Method". In the next step select "9700 Max Mode" and then enter the PCR profile as outlined below.

Other thermal cyclers:
The following ramping rates must be applied: heating 1,6 ˚C/s, cooling 1,6 ˚C/s.

Amplification Area:
Program the Thermal Cycler for amplification according to the following thermal profile (consult the User´s Manual for additional information on programming and operation of the thermal cycler):

95°C 15 min
94°C; 0,5 min -> 62°C; 1 min -> 72°C; 1 min for 25 cycles
72°C 15 min
4°C FOREVER



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1. Set reaction volume to 13 µL.
2. Set the appropriate ramping rates (heating 1,6 ˚C/s, cooling 1,6 ˚C/).
3. Start the amplification (duration approximately 2,5 hrs).
4. Following amplification, remove the tubes containing completed PCR amplification reaction from the thermal cycler and place into a suitable holder. Centrifuge briefly to collect the content. Remove the caps carefully to avoid aerosol contamination. Do not bring amplified material into the pre-amplification areas. Amplified material should be restricted to amplification and detection areas.

7.3 Detection

Sample Preparation

Refer to the respective Life Technologies/ABI Genetic Analyzers User Manual for instructions on maintenance and handling. Prior to running the Devyser Thrombophilia kit, the instrument must be spectrally calibrated to support detection of the Dye-Set DEV-5. See section 4.3 for details.

Sample Preparation for Capillary Electrophoresis

1. Prepare a loading cocktail by combining and mixing 2 µL of the size standard (e.g. 560 SIZER ORANGE) with 100 µL Hi-Di™ Formamide (sufficient mix for 6 wells/tubes).
2. Vortex for 15 seconds.
3. Dispense 15 µL of the loading cocktail into the required number of wells of a microwell plate or into individual tubes to be placed on the Genetic Analyzer.
4. Add 1,5 µL of the sample PCR product to the corresponding well/tube containing loading cocktail.
5. Seal the plate/tubes.

Instrument Preparation

Create a sample sheet using the data collection software with the following settings:

- Sample ID
- Dye-Set: Any5Dye/DEV-5
- Recommended run Module: See below for different polymers and instruments

Run Modules

The amount of PCR product injected into the capillaries can be adjusted by increasing/decreasing the injection time and/or injection voltage.

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ABI 310(Run with module file "GS STR POP4 (1 mL) G5.md5")

Run Parameters	*POP-4*
Capillary length	47 cm
Run temperature	60 ˚C
Injection voltage	10 kV
Injection time	5 s
Run voltage	15 kV
Run time	30 min

ABI 3100/3130

Run Parameters	*POP-4/POP-7*
Capillary length	36 cm
Run temperature	60 ˚C
Injection voltage	1,5 kV
Injection time	20 s
Run voltage	15 kV
Run time	1500 s

ABI 3500

Run Parameters	*POP-7*
Capillary length	50 cm
Run temperature	60 ˚C
Injection voltage	1,6 kV
Injection time	15 s
Run voltage	19,5 kV
Run time	1500 s

ABI 3730

Run Parameters	*POP-7*
Capillary length	36 cm
Run temperature	60 ˚C
Injection voltage	1,6 kV
Injection time	15 s
Run voltage	15 kV
Run time	1500 s

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8. Data Analysis

Background to data analysis

An individual has two copies (alleles) of each of the investigated loci and is considered being homozygous for a given DNA sequence when both alleles have the same sequence. An individual is considered being heterozygous for a given DNA sequence when the two alleles differ in sequence.

8.1 The Devyser Thrombophilia kit

The Devyser Thrombophilia kit is used for the qualitative analysis of mutations in the loci outlined in tables 1 and 2. Analysis of the different alleles is performed using one single amplification mix (Thromb Mix). All detected normal and mutant alleles are listed in tables 1 and 2.

Normal alleles

PCR fragments representing normal DNA sequences are detected in the blue channel as outlined in table 1 below.

Mutant alleles

PCR fragments representing mutant DNA sequences are detected in the green channel as outlined in table 2 below.

8.2 Data interpretation

Normal (non mutated) alleles

The sample is to be considered normal for a certain locus if a normal allele fragment is detected while the corresponding mutant allele fragment is absent (Figure 8.1).

Heterozygous mutation

The sample is to be considered heterozygously mutated in a certain locus if both a normal allele fragment and the corresponding mutation allele fragment are present (Figure 8.2).

Homozygous mutation

The sample is to be considered homozygously mutated in a certain locus if the normal allele fragment is absent, while the corresponding mutant allele fragment is present (Figure 8.3).

Peak cutoff signals (rfu)

It is recommended that an instrument specific cutoff range is determined. Do not to use lower cutoff values than 200 rfu (ABI 310, 3100 and 3130) and 500 rfu (ABI 3730, 3500). Do not analyse samples where peak signals are saturated.

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Figure 8.1. Homozygous wildtype MTHFR 1298 (1298A)

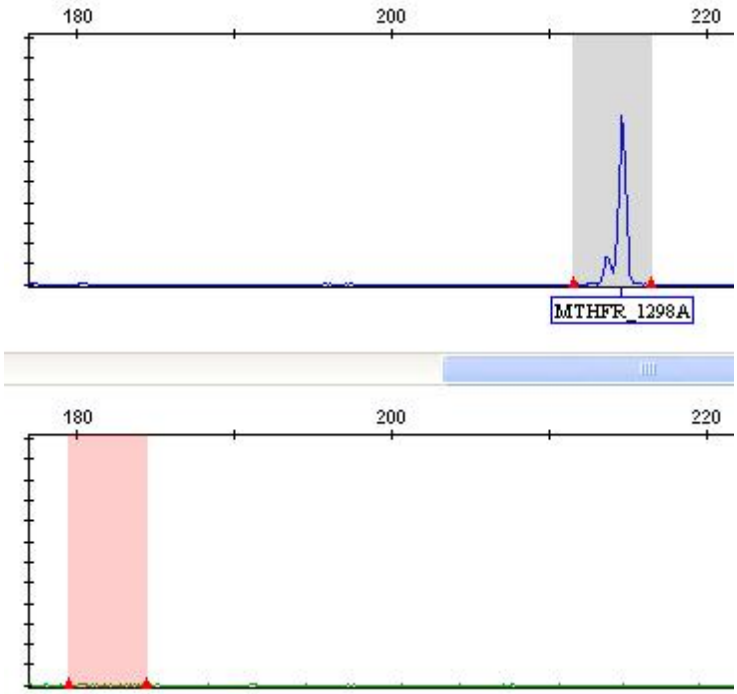

Figure 8.2. Heterozygous MTHFR 1298 (1298A/1298A>C)

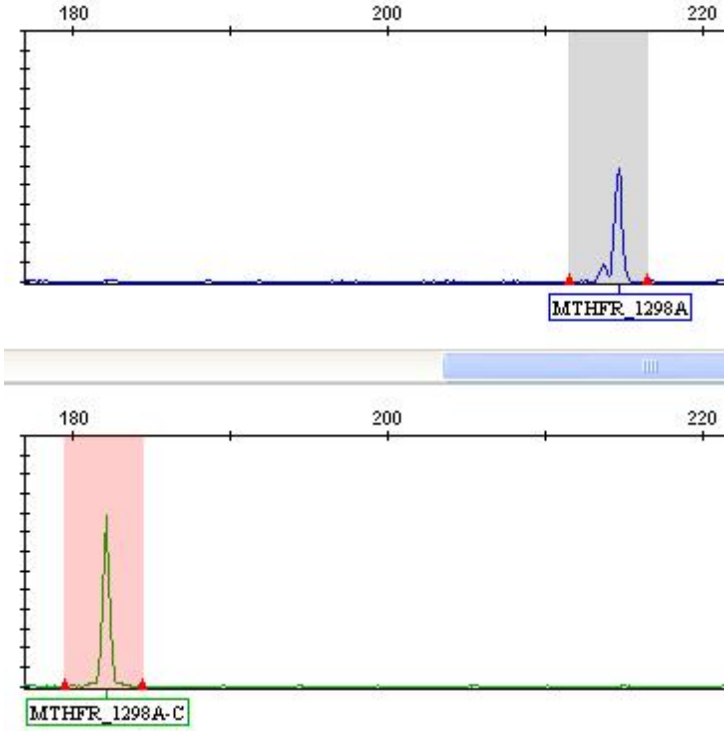

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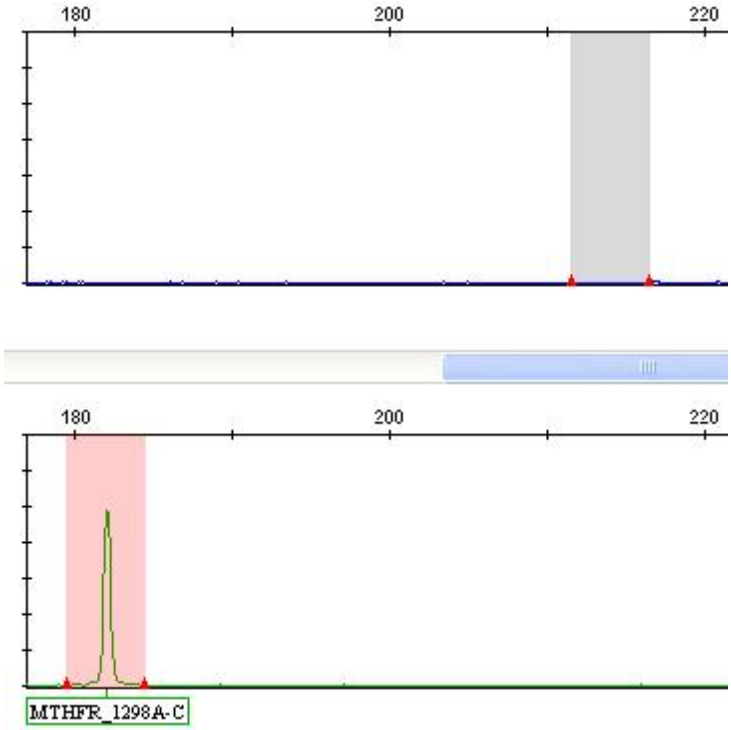
Figure 8.3. Homozygous mutated MTHFR 1298 (1298A>C)



Sizing of DNA fragments

PCR fragments obtained using the Devyser Thrombophilia kit should be sized with the 560 SIZER ORANGE using a fragment analysis software (e.g. GeneMapper).

Table 1. Normal alleles detected

Normal alleles, their expected PCR fragment length and dye colour.

Gene	Allele	Size (bp)*	Colour
Methyltetrahydrofolate Reductase (MTHFR)	1298A	215	Blue
Plasminogen Activator Inhibitor 1 (PAI-I/SERPIN 1)	5G	233	Blue
Methyltetrahydrofolate Reductase (MTHFR)	677C	295	Blue
Factor II (Prothrombin)	20210G	312	Blue
Factor V (R2)	4070A	381	Blue
Factor V (Leiden)	1691G	437	Blue

*Allele fragment lengths given in this table are based on average observed fragment lengths obtained using ABI3130 and ABI3500, POP-7 polymer and 560 SIZER ORANGE. Allele fragment size ranges may vary depending on the instrument, polymer type and size marker used during electrophoresis.

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Table 2. Mutant alleles detected

Mutant alleles, their expected PCR fragment length and dye colour.

Gene	Allele	Size (bp)*	Colour
Factor V (Leiden)	1691G>A	125	Green
Plasminogen Activator Inhibitor 1 (PAI-I/SERPIN 1)	4G	134	Green
Methyltetrahydrofolate Reductase (MTHFR)	677C>T	151	Green
Methyltetrahydrofolate Reductase (MTHFR)	1298A>C	182	Green
Factor V (R2)	4070A>G	388	Green
Factor II (Prothrombin)	20210G>A	426	Green

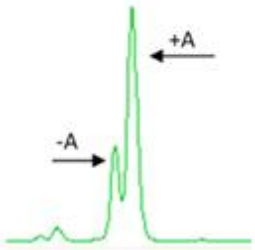
*Allele fragment lengths given in this table are based on average observed fragment lengths obtained using ABI3130 and ABI3500, POP-7 polymer and 560 SIZER ORANGE. Allele fragment size ranges may vary depending on the instrument, polymer type and size marker used during electrophoresis.

8.3 Troubleshooting

PCR Artefacts

-A peaks (figure 8.4) are detected as extra peaks that is one base pair shorter than the full length (+A peak) PCR product.

Figure 8.4. -A and +A peaks as indicated by the arrows.



Electrophoretic Artefacts

Crosstalk/bleed through between dye channels may occur during detection (Figure 8.5). Cross-talk appears as equally sized peaks in neighbouring dye channels and should be excluded from the analysis.

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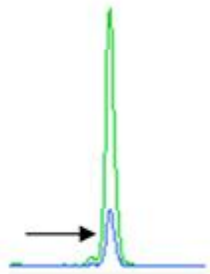
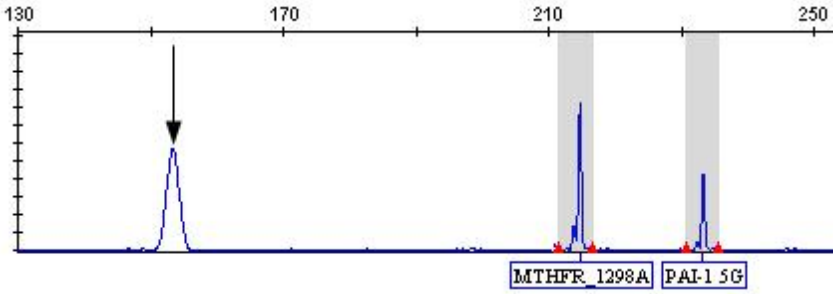
Figure 8.5. Crosstalk peak (from green to blue channel) as indicated by the arrow.



Dye blobs may appear in the sample analysis range (figure 8.6). In general, dye blobs appear as broad, undefined peaks of a single colour and tend to occur relatively early in the data.

Figure 8.6. Dye blob as indicated by the arrow



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9. Performance Characteristics

Sensitivity

Definition: The proportion (%) of subjects with a well defined genetic condition and whose test values are positive within the defined decision limit.

Experimental design:
One hundred (100) DNA samples previously characterised to carry at least one of the listed mutations (chapter 8, table 2) were tested using Devyser Thrombophilia. All results obtained using Devyser Thrombophilia correlated with the previously obtained results.

Result: >99% sensitivitya

Specificity

Definition: The proportion (%) of subjects who do not have a well defined genetic condition and whose test results are negative or within the defined decision limit.

Experimental design:
One hundred one (101) DNA samples previously characterised to carry at least one copy of all the listed normal alleles (chapter 8, table 1) were tested using Devyser Thrombophilia.All results obtained using Devyser Thrombophilia correlated with the previously obtained results.

Result: > 99% specificity

Reproducibility

Within run reproducibility

Definition: The degree (%) of agreement between measurements conducted on replicate specimens
of the same measured where the measurements are carried out under unchanged conditions.

Experimental design: Forty-eight (48) replicates of a normal male sample was amplified in one run using identical reagent batches, operator, PCR- and capillary electrophoresis instruments. All 48 replicates gave the expected results.

Result: >98 % within run reproducibility

Between run reproducibility

Definition: The degree (%) of agreement between measurements conducted on replicate specimens of the same measurand where the measurements are carried out under changed

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conditions.

Experimental design: One hundred and nine (109) replicates of a normal male sample were amplified on 3 different occasions using different reagent batches, operators, PCR- and capillary electrophoresis instruments. All 109 replicates gave the expected results.

Result: >99 % between run reproducibility

Clinical Evaluation

One hundred and three (103) DNA samples previously characterised for at least one of the parameters analysed by Devyser Thrombophilia were tested blind. All samples were successfully analysed. Results are summarised in table 1 below.

Table 1. Results from the clinical evaluation of 103 previously characterised clinical samples

Locus	Number of samples	Correlation (%)
Factor V G1691 (Leiden)		
wt/wt	81	100
wt/mut	14	100
mut/mut	4	100
Plasminogen Activator Inhibitor 1 (PAI-I/SERPIN 1)		
wt/wt	16	100
wt/mut	22	100
mut/mut	21	100
Methyltetrahydrofolate Reductase (MTHFR) C677		
wt/wt	31	100
wt/mut	49	100
mut/mut	14	100
Methyltetrahydrofolate Reductase (MTHFR) A1298		
wt/wt	42	100
wt/mut	43	100
mut/mut	10	100
wt/wt	85	100
wt/mut	8	100
mut/mut	4	100
Factor V H1299 (R2)		
wt/wt	77	100
wt/mut	12	100
mut/mut	6	100

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Cross Reactivity

No cross reactivities have been observed.

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10. Procedural Limitations

A.

Use of this product should be limited to personnel trained in the techniques of PCR and capillary electrophoresis.

B.

The Devyser Thrombophilia kit has been validated using Life Technologies/ABI Thermal Cycler GeneAmp® 9700 and Life Technologies Veriti® Thermal cycler. It is recommended that alternative thermocycler instruments are thoroughly evaluated with the Devyser Thrombophilia kit prior to the results being used for diagnostic use.

C.

The Devyser Thrombophilia kit has been validated using QIAamp DNA Blood Mini Kit for extraction of DNA from human whole blood. Performance with other matrices and DNA extraction kits has not been validated and may result in false negative or false positive results.

D.

Devyser Thrombophilia kit should be used only for the detection of specific mutations according to the instructions for use. Many other mutations are possible that may not be detected using Devyser Thrombophilia. The assay has not been validated for diagnosis of Thrombophilia. Results obtained with Devyser Thrombophilia kit can only be directly applied to the tissue or specific sample material tested.

E.

Only the following mutations are tested: Factor V G1691A, Factor V H1299R, Prothrombin G20210A, PAI-1/SERPIN1 4G/5G, MTHFR C677T and MTHFR A1298C.

F.

Diagnostic errors can occur due to rare sequence variations.

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11. Notice to Purchaser

Results from Devyser Thrombophilia should be interpreted with consideration of the overall picture obtained from clinical and laboratory findings. Devyser AB will not accept responsibility for any clinical decisions taken.

LIZ®, Veriti® and GeneAmp® are registered trademarks of Life Technologies Corporation. GeneScan™, POP-4™, POP-7™ and Hi-Di™ are trademarks of Life Technologies Corporation.

Purchase of this product does not provide a license to perform PCR under patents owned by any third party.

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